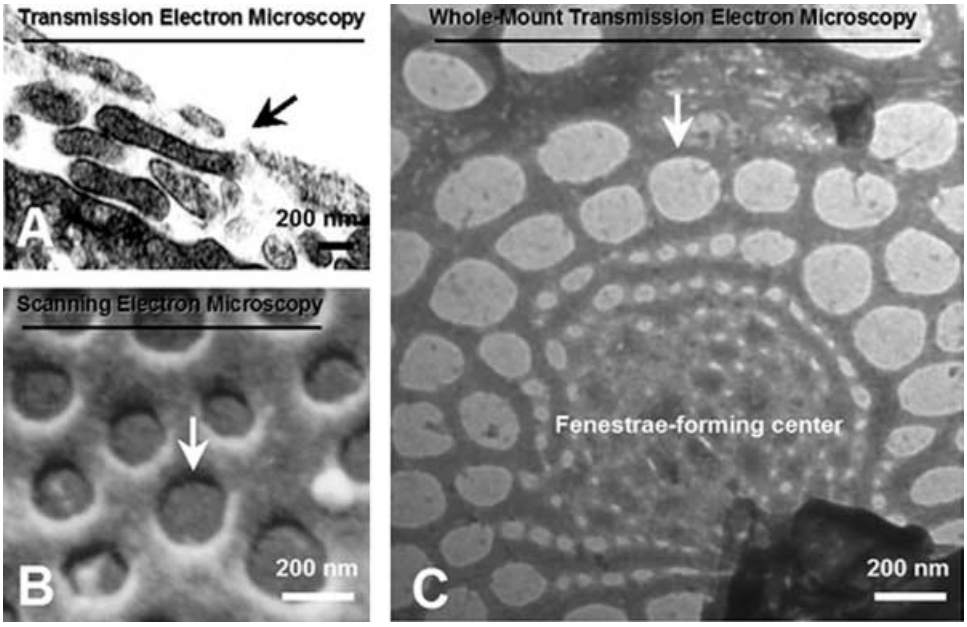

Fig. 1. High magnification electron micrographs of rat hepatic endothelial fenestrae. (*A*) Transmission electron microscopy image of sectioned hepatic endothelial cells *in situ*, showing the fenestrated, processes (arrow) and the histologic relationship with the numerous microvillous processes of the liver parenchymal cells situated in the space of Disse. (*B*) Scanning electron micrograph of the fenestrated cytoplasm of hepatic endothelial cells *in vitro*. Notice the fenestrae (arrow) on the cell surface. (*C*) Whole-mount transmission electron micrograph of the fenestrated cytoplasm (arrow) of a hepatic endothelial cell cultured on transmission electron microscopy grids, disclosing the process of fenestrae formation. Note the area of intermediated density from which rows of fenestrae with increasing diameter are radiating into the surrounding cytoplasm. Scale bars, 200 mm.

endothelium were completely devoid of caveolin-1, similar to the report by Esser et al [9] for the choroid plexus endothelium. Now, our experiments leave open the possibility that fenestrae in other vascular beds could represent fused caveolae, and that caveolar precursor vesicles lacking caveolin-1 could fuse to form fenestrae. But if caveolae are defined as specialized plasma membrane invaginations stabilized by caveolins, then our findings in caveolin-deficient mice seem to prove that fenestrae in glomerular endothelium cannot represent fused caveolae.

BARBARA J. BALLERMANN
Edmonton, Alberta, Canada

Correspondence to Barbara J. Ballermann, Director of Nephrology, University of Alberta, Edmonton, Alberta, Canada.
E-mail: barbara.ballermann@ualberta.ca

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Immunosuppressive and calcimimetic drug-drug interactions

To the Editor: Drug-drug interactions (DDIs) are an important cause of adverse drug reactions. It has been estimated that approximately 5% of prescribing errors [1] or of adverse drug reactions [2] are caused by DDIs in

Table 1. Calcimimetic and immunosuppressive drug-drug interactions through cytochrome P450 (CYP) and transporters

	Metabolic pathway		
	CYP		
Drugs	Inductor or substrate	Inhibitor	Transporters
Calcimimetic drugs			
Cinacalcet	1A2, 3A4	2D6	?
Immunosuppressive drugs			
GCs	3A4		P-gp, MRP, OATP
AZA			
MMF	3A4		
CsA		3A4	P-gp OATP MRP2
FK		3A4	P-gp OATP
Siro		3A4	P-gp OATP

Abbreviations are: AZA, azathioprine; CsA, cyclosporine; FK, tacrolimus; GCs, glucocorticoids; MMF, mycophenolate mofetil; Siro, sirolimus, Pgp, glycoprotein, OATP, hepatocyte-specific organic anion uptake transporter.

hospitalised patients. Mechanisms of drug-drug interaction include competitive interaction between two drugs that are metabolized via the same enzyme system [for example, cytochrome P450 (CYP)] or a competition for the same active transport system, such as P-glycoprotein (P-gp) or organic anion transporter peptide (OATP).

Cinacalcet is becoming the cornerstone of the end-stage renal disease (ESRD) therapy to reduce parathyroid hormone levels in patients with secondary hyperparathyroidism who are receiving hemodialysis, and to ameliorate disturbances in serum calcium and phosphorus [3]. Indeed, more ESRD patients may undergo renal transplantation with this medication.

Although immunosuppression is required for graft maintenance, it is unknown how and to what extent the antirejection therapies will interact with the calcimimetic medication. Cinacalcet is metabolized by multiple enzymes, primarily the CYP3A4, CYP2D6, and CYP1A2. In addition, they may also inhibit the 2D6 enzyme's activity [4]. Since cyclosporine, tacrolimus, and sirolimus, the most popular immunosuppressive therapies, share the same metabolic pathway [5], significant drug-drug interactions may occur when these medications are given concomitantly. Table 1 summarizes those potential DDIs.

Physicians should be aware for the potential drug-drug interactions between calcimimetic and immunosuppressive agents.

HASSANE IZZEDINE, VINCENT LAUNAY-VACHER, SVETLANA KARIE, and GILBERT DERAY
Paris, France

Corresondence to Hassane Izzedine, M.D., Department of Nephrology, Pitie-Salpetriere Hospital, 47-83, Blvd de l'Hopital, 75013 Paris. E-mail: hassan.izzedine@psl.ap-hop-paris.fr

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